REMARKS

Claims 30-37 are cancelled without prejudice or disclaimer, and new claims 38-47 are added. The new claims are fully supported by the specification as filed. T cells comprising a DNA molecule encoding a chimeric immunoglobulin/T cell receptor or a chimeric immunoglobulin/CD3 protein are described throughout the specification and the claims as filed. A variable region of this chimeric molecule that binds a tumor-associated antigen (TAA) or an antigen associated with an infectious agent also is described throughout the specification, including the description found in the claims as originally filed. Humanized versions of the variable regions of such antibodies also are described throughout the specification, for instance at page 4, lines 20-21, page 8, line 13, page 12, lines 18-22, and especially with reference to the use of a human variable region at page 14, line 27 through page 15, line 9. In particular, Example 2 exemplifies a humanized anti-CEA antibody, hMN-14, which is made through the grafting of a complementary-determining region (CDR) of the mouse MN-14 antibody onto a human Ig backbone. Example 3 exemplifies an anti-idiotypic antibody, WI2, that recognizes a humanized anti-CEA antibody. Treatment with both these antibodies is shown in Example 4.

The concurrent use of modified T-cells and cytokines, such as interleukin-2, is described at page 6, line 28, or page 30, for example, and supports a claim directed to a pharmaceutical composition comprising both a transformed T-cell and a cytokine. Reconsideration and reexamination are respectfully requested in view of the foregoing amendments and the following comments.

The amendment to the specification clarifies that a source of written description for making the MN-14 antibody is U.S. Patent No. 5,874,540, ("the '540 patent) to Hansen. Hansen *et al.*'s 1993 research publication is no longer exclusively relied upon in this context because MN-14 was a proprietary cell line of Immunomedics, Inc. when this paper was published. An enclosed copy of the '540 patent shows in column 5, lines 61-67 that the murine anti-CEA IgG1 monoclonal antibody MN-14 disclosed in this patent were previously described in Hansen *et al.*, *Cancer* 71: 3478 (1993), which is referenced in the present specification as disclosing the murine MN-14 monoclonal antibody. The '540 patent provides a fully enabling description to make this antibody by artificial synthesis of its encoding DNA, for example.

Rejection under the judicially created doctrine of double patenting

Claims 30-37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 6,132,718. Applicant

will address this rejection appropriately with respect to claims 38-47, upon indication of allowable subject in the instant application.

Rejection under 35 U.S.C. § 103(a)

Method claims 30-37 are rejected under 35 U.S.C. § 103(a) as obvious over Eshhar *et al.*, *Proc. Nat'l Acad. Sci. USA* **90:** 720 (1993), WO 92/15322, Wagner *et al.*, *Biotech. Therap.* **3:** 81 (1992), and "applicant's admission" at page 22 of the specification, in view of Hansen *et al.*, *Cancer* **71:** 3478 (1993) ("Hansen"). Applicant traverses the rejection insofar as it relates to the new product claims 38-47.

The Examiner's reviewing court sets aside actions by the USPTO that are unsupported by substantial evidence in a case reviewed on the record of an agency hearing provided by statute. *In re Lee*, 277 F.3d 1338, 1342 (Fed. Cir. 2002) (citing 5 U.S.C. § 706[2][B]). For meaningful judicial review, the agency must articulate the reasons for its decisions. *Id.* In the context of a rejection under 35 U.S.C. § 103, this requirement obliges the Examiner to provide a motivation to combine references in the "objective evidence of record." *Id.* at 1343. Specifically, the motivation to combine references must "not be resolved on subjective belief and unknown authority." *Id.* at 1344. Instead, the Examiner must rely on a "specific hint or suggestion in a particular reference" to motivate the combination of references, without which the rejection is legally erroneous and constitutes an arbitrary agency action. *See Id.*

Eshhar allegedly teaches T cells that are transfected with an Ig/TCR chimera, where the Ig moiety binds a desired antigen (*i.e.*, Eshhar's T cell would correspond to a T3 cell). The examiner alleges that it would have been obvious to one of ordinary skill in the art at the time of the invention to use Eshhar's T cells to treat tumors or infections, because WO 92/15322 teaches the efficacy of an Ig/TCR chimera to treat tumors and infections and Wagner allegedly teaches the approach of tumor immunotherapy by the activation of the idiotypic network. Further, Hansen is applied to show that CEA is a TAA. The Examiner alleges that in combination, the prior art suggests adoptive immunotherapy to treat tumors and infectious diseases.

The examiner admits that Eshhar does not teach or suggest a specific showing that the chimeric gene can be used in adotive immunotherapy, a specific showing that the immunoglobulin can be used to recognize a TAA or a disease caused by an infectious agent and the use of cytokines and/or administration of an anti-ID and the specific use of CEA. The examiner alleges that the secondary references provide these missing teachings of Eshhar.

The rationale for combining Eshhar and WO 92/15322 with Wagner and Hansen is legally insufficient, because the suggestion to combine the references is based on hindsight reasoning

The examiner motivates the transfected T-cells by Eshhar that allegedly uses the chimeric genes in adoptive immunotherapy and in view of WO 92/15322, which allegedly shows that such chimeric genes can be used in diseases caused by either tumors or infectious agents. While various elements of the claimed methods have been shown to be disclosed in the art, the examiner provides no impetus to combine the various components of the transfected T-cells in the manner claimed.

The rejection resembles closely that applied in the application of Levengood, regarding which the Board of Patent Appeals and Interferences stated the following:

> At best, the examiner's comments regarding obviousness amount to an assertion that one of ordinary skill in the relevant art would have been able to arrive at appellant's invention because he had the necessary skills to carry out the requisite process steps. This is an inappropriate standard for obviousness. See *Orthokinetics Inc. v. Safety Travel Chairs Inc.*, 806 F.2d 1565, 1 USPQ2d 1081 (Fed. Cir. 1986) (citing an inappropriate determination of obviousness based on what the artisan "would have been able to produce"). . . .
>
> Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). *In re Newell*, 891 F.2d 899, 13 USPQ2d 1248 (Fed. Cir. 1989). Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done.

Ex parte Levengood, 28 USPQ2d 1300, 1301-1302 (BPAI 1993) (parenthetical material added). As in *Levengood*, the examiner has located references describing various aspects of the claimed invention but has provided no motivating force to combine the references. The examiner only alleges that "it was within the purview of one skilled in the art [to] combine two treatment techniques, it also would have been obvius to induce the idiotypic network (as described by Wagner et al) in combination with adoptive immunotherapy technique of Eshhar et al." This remark is no different than asserting that the artisan "had the necessary skills to carry out the requisite process steps," which the Board found an inappropriate standard for determining *prima facie* obviousness in *Levengood*.

Rather than suggesting inducing an integrated immune response according to the claimed invention, the cited art teaches away from the claimed invention

When assessing what a reference would have suggested to the artisan of ordinary skill,[1] it can be instructive to see what the data suggested to the authors, themselves. Eshhar motivates using his transfected T cells as an alternative to inducing a humoral response, an in fact, directly kills the target cells. In the context of comparing the relative inefficiency of humoral immunity in resolving particular disease states, Eshhar remarks: "Cell-mediated immunity **rather than** humoral antibody production is primarily responsible for the rejection of allografts, virus infected cells and malignant tissues" (emphasis added). Eshhar *et al.* (1990) *Br. J. Cancer* **62**, Suppl. X, 27-29, at page 27, first column (reference A9 of the IDS filed December 17, 1998 in the parent application). Eshhar would not have suggested an integrated immune response by inducing both cellular and humoral immunity. Eshhar further states:

> This approach exploits the scFv as the antigen-recognition unit and the potent cytotoxic responses of NK cells and T cells and/or the ability of T cells to secrete lymphokines and cytokines upon activation at the target site, thus recruiting, regulating, and amplifying other arms of the immune system.
>
> Finally, this approach can be applied to anti-idiotypic vaccination by using helper T cells expressing chimeric receptors made of Fv of anti-idiotypic antibodies. Such 'designer lymphocytes' will interact and stimulate idiotype-bearing B cells to produce antigen-specific antibodies, thus bypassing the need for active immunization with toxic antigens.

Eshhar *et al.* (1993) *Proc. Natl. Acad. Sci. USA* **90**:720-724, at 724. Eshhar's suggestion to "recruit . . . other arms of the immune system" would have suggested that humoral immunity can be induced **solely** as a result of administration of transfected T cells. Further, Eshhar suggests that active immunization (vaccination) can be **bypassed** by administration of the transfected T cells. This hardly would have supplied an impetus to the artisan of ordinary skill to induce an integrated cellular and humoral immune response by administering **both** T cells expressing chimeric Ig/TCR or Ig/CD3 and the prescribed vaccine.

Thus, the rejection is based only on what the specification discloses to the examiner, not what the prior art would have suggested to the artisan of ordinary skill. The rejection is based on the hindsight afforded by the specification, which is an improper basis for a determination of

[1] In the Office Action, the standard for determining *prima facie* obviousness inadvertently is based on what the *skilled* artisan would have inferred.

prima facie obviousness. *In re Fine, loc. cit.* Eschhar in combination with the secondary references fail to render the presently claimed invention obvious, and the rejection should be withdrawn accordingly.

Further, the presently claimed invention contains claims (claims 40 and 45) that are directed to a transfected T-cell comprising a DNA encoding the variable regions of a humanized antibody that binds a TAA or an antigen associated with an infectious agent. The cited art discusses general aspects of the claimed technology, but the Examiner has pointed to no language in any of these publications that discusses or suggests the advantage of humanizing the variable region of the antibody used to create a chimeric immunoglobulin/T cell receptor or a chimeric immunoglobulin/CD3 protein, which is realized in the instantly claimed invention. Without such a suggestion provided by the references of record, an obviousness rejection cannot be sustained. *Supra*. Such T-cells would result in less than of an immune response from the subject injected with the cells.

CONCLUSION

In view of the foregoing, it is respectfully urged that the present claims are in condition for allowance. An early notice to this effect is earnestly solicited. Should there be any questions regarding this application, the Examiner is invited to contact the undersigned at the telephone number shown below.

Respectfully submitted,

April 26, 2002
Date

Brian K. Lathrop
Agent for Applicant
Reg. No. 43,740

Reg. No. 34,485

FOLEY & LARDNER
Suite 500, 3000 K Street, N.W.
Washington, D.C. 20007-5109
(202) 672-5300

Marked-up copy of amendment showing changes made:
Pages 13-14

An example of a suitable Mab is a Class III anti-CEA Mab. Conventional antisera raised against CEA usually contain antibodies that react with a group of substances closely related to CEA. The major members of this family of CEA-related antigens are (1) the normal cross-reactive antigen (NCA), which shares a similar tissue distribution with CEA, and (2) meconium antigen (MA), which shares almost identical physiochemical properties with CEA. The first panel of monoclonal antibodies (MAb) that defined NCA-cross-reactive, MA-cross-reactive, and CEA-specific epitopes on the CEA molecule were described by Primus *et al., Cancer Research 43*: 686 (1983). In particular, three classes of anti-CEA antibody were identified: 1) Class I antibodies, which react with CEA, NCA and MA; 2) Class II antibodies, which react with CEA and MA, but not with NCA; and 3) Class III antibodies, which are specific for CEA and do not bind with NCA or MA. Methods for obtaining Class III anti-CEA MAbs are disclosed by Primus *et al., Cancer Research 43*: 686 (1983), and Primus *et al.*, U.S. patent No. 4,818,709. Moreover, the production of second generation Class III anti-CEA MAbs is disclosed by Hansen *et al., Cancer 71*: 3478 (1993), **and U.S. Patent No. 5,874,540,** which [is] **are** incorporated by reference.

Pages 30-31

The production of MN-14, a Class III, anti-CEA MAb, has been described by Hansen *et al., Cancer 71*: 3478 (1993), which is incorporated by reference **and in U.S. Patent No. 5,874,540**. Briefly, a 20 gram BALB/c female mouse was immunized subcutaneously with 7.5 μg of partially-purified CEA in complete Freund adjuvant. On day 3, the mouse was boosted subcutaneously with 7.5 μg of CEA in incomplete Freund adjuvant and then, the mouse was boosted intravenously with 7.5 μg of CEA in saline on days 6 and 9. On day 278, the mouse was given 65 μg of CEA intravenously in saline and 90 μg of CEA in saline on day 404. On day 407, the mouse was sacrificed, a cell suspension of the spleen was prepared, the spleen cells were fused with murine myeloma cells, SP2/0-Ag 14 (ATCC CRL 1581) using polyethylene glycol, and the cells were cultured in medium containing 8-azaguanine. Hybridoma supernatants were screened for CEA-reactive antibody using an ^{125}I-CEA radioimmunoassay (Roche; Nutley, NJ). Positive clones were recloned.